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Cancer-Producing Hydrocarbons

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THE widespread interest during the past twenty-five years in the cancer-producing activity of certain polynuclear aromatic hydrocarbons may be traced to at least three observations: (1) that continued application of a coal-tar fraction to the ear skin of rabbits would produce skin cancer; (2) that certain classes of industrial workers, who were constantly in contact with coal tar, soot, or similar matter, were peculiarly susceptible to skin cancer; (3) that certain bile acids could be converted *in vitro* to the carcinogen, methylcholanthrene (I).

After an extremely tedious fractionation of coal-tar concentrates, a group of English workers isolated and identified benzo[a]pyrene (II) as the active carcinogen. In connection with this work the group prepared dibenz[a,h]anthracene (III), the first carcinogenic hydrocarbon to be obtained by purely synthetic methods.

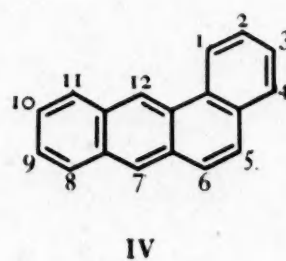
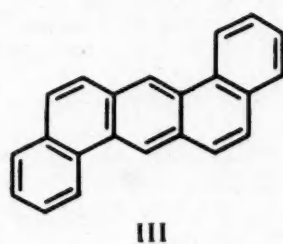
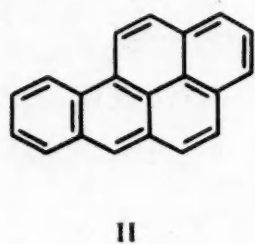
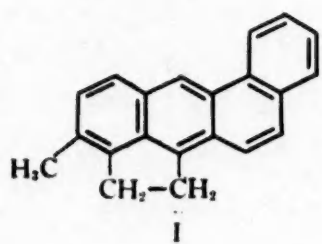
By a cancer-producing compound is

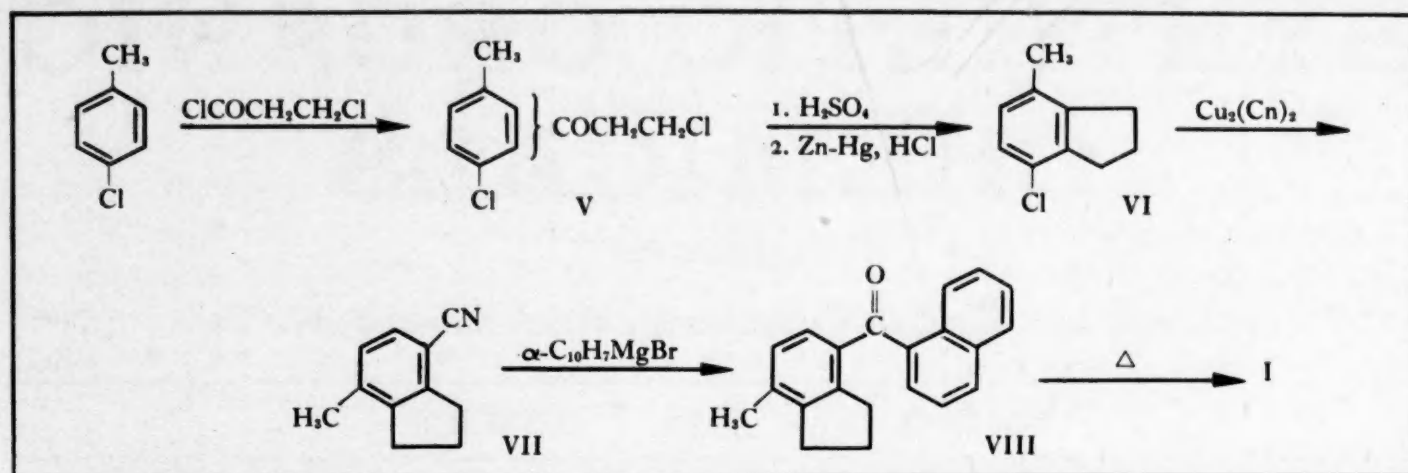
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meant one which will produce certain characteristic growths when applied to mice. There are two methods of testing for carcinogenic activity. In one method a benzene solution of the compound is painted repeatedly on the skin of a mouse and the effect observed. In the other method of testing, an incision is made and a pellet containing the compound to be tested is inserted under the skin and any cancerous growth noted. In some cases, there may be a considerable difference when the potency of a compound as determined by the painting technique is compared with the result obtained by the injection method.

Benz[a]anthracene Derivatives

A consideration of the formulas for the carcinogenic hydrocarbons mentioned earlier shows that all are derivatives of the parent substance, benz[a]anthracene (IV). Thus, benzo[a]pyrene is benz[a]anthracene with substitution at the 1,12 position, and methylcholanthrene is benz[a]anthracene substituted at the



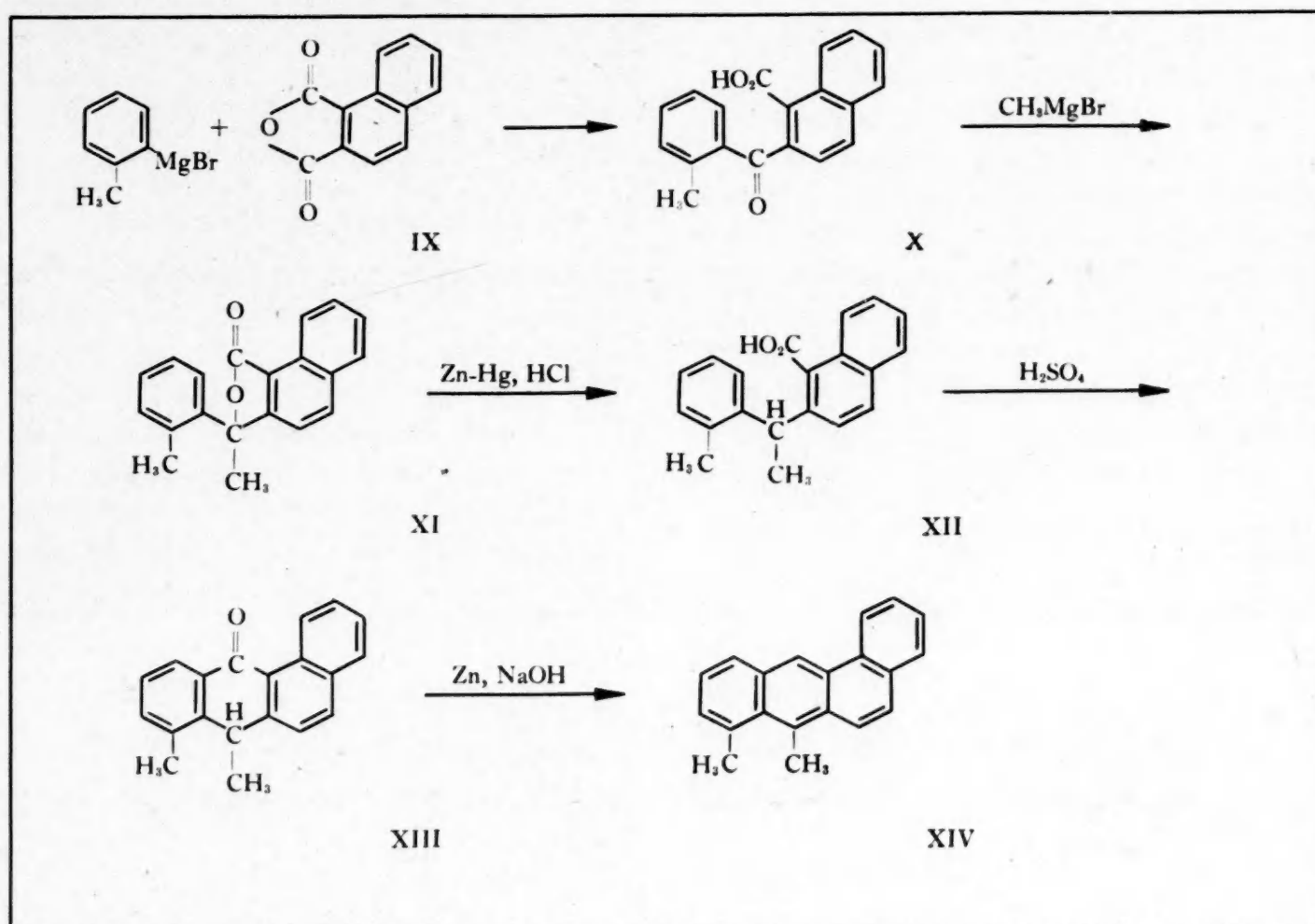


7,8,9 positions. Through the quantity of synthetic work that has been completed on the derivatives of benz[a]anthracene, it has been found that it is only those compounds having a substituent at the 7, 8, or 12 position which are potent carcinogens. It is difficult to give an exact comparison of potency, but the more important hydrocarbons may be listed as follows, in the order of decreasing ability to produce cancer in mice: methylcholanthrene, cholanthrene (I minus CH_3), 7-methyl-benz[a]anthracene, benzo[a]pyrene, and dibenz[a,h]anthracene.

With the exception of a few compounds, e.g., benzo[c]phenanthrene, all the hydrocarbons found to produce cancer in mice are derivatives of benz[a]anthracene. However, in addition to hydrocarbons, there are also other types of compounds which have been found to have a similar effect.

Synthesis of Benz[a]anthracene Derivatives

Entirely apart from their biological effect, these compounds are of considerable interest because of the methods



that have been used for their synthesis from relatively simple starting materials. In order for results to be significant, these polynuclear compounds must be constructed by methods which will allow no doubt concerning the positions of substituent groups.

In making methylcholanthrene (I), *p*-chlorotoluene was condensed with β -chloropropionyl chloride, in the Friedel-Crafts reaction, to give a mixture of two chloroketones (V). Following cyclization of the chloroketones to the corresponding hydrindones, the latter were reduced by the Clemmensen method to 4-chloro-7-methylhydrindene (VI). The nitrile (VII) was formed from VI by reaction with cuprous cyanide in pyridine. Condensation of this nitrile with α -naphthylmagnesium bromide then gave the ketone (VIII), which was pyrolyzed by the Elbs reaction to methylcholanthrene, I.

In a further example of this synthetic work, 7,8-dimethyl-benz[a]anthracene was prepared by starting with 1,2-naphthalic anhydride (IX). On reaction with *o*-tolylmagnesium bromide, this gave a mixture of acids from which the desired keto acid (X) was isolated. The lactone which was obtained by treating this acid with methylmagnesium bromide was reduced by amalgamated zinc and hydro-

chloric acid to the acid (XII). This acid was cyclized with concentrated sulfuric acid to an anthrone (XIII), which, upon reduction with zinc dust and alkali, gave the desired hydrocarbon (XIV).

After a polycyclic hydrocarbon has been made and found to be cancer producing, it may be used to induce experimental cancer in mice. Such controlled production of cancer is of value in that all stages of the growth can be watched and examined. Also, possible curative agents can be tested advantageously when the cancer is produced in the animal under such controlled conditions.

NOTE: The nomenclature and numbering used in this paper are in accord with the "Ring Index" of Patterson and Capell, A.C.S. Monograph No. 84.

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A Simple Automatic Recording Calorimeter

By L. K. J. TONG*

THE method described here utilizes the heat evolved from a reaction to vaporize a liquid, whose loss in weight is automatically recorded.

The apparatus, shown schematically in Figure 1, over the page, was designed originally to measure the heat evolution accompanying polymerization processes.¹ However, it may be adapted to study other types of organic reactions where the reaction rates are reasonably

slow and the heats evolved are large. The limiting conditions for maximum accuracy require the reaction studied to evolve approximately one kcal. to one-quarter kcal. within a time interval between one-half and six hours. In other words, if 0.05 mole of reactant is used, the reaction should have a ΔH value between 20 kcal./mole and 5 kcal./mole. During the above-mentioned time interval, the reaction should be at least 90 per cent complete; the extent of reaction should be determinable, of course, by some analytical means.

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¹J. Am. Chem. Soc. 67, 1278 (1945).

Calorimeter:

The calorimeter, shown in Figure 1, is essentially an all-glass refluxing apparatus. The inner jacket has a one-fourth-inch opening (K) at the bottom to permit passage of vapor. Inside the jacket, a vacuum tube (E) is suspended freely from a balance by means of a fine Ni-chrome wire fastened on two glass hooks sealed on the outside of the tube (E). This tube contains a reaction tube (H) which is totally submerged in the boiling liquid. The reaction tubes are made from 18mm. Pyrex tubing. The sides, while being softened by a pointed flame, were pushed in with capillary tubing to increase the surface area and at the same time to provide capillaries which promote smooth boiling.

During the runs, the tube (E) is loosely covered with a hollow glass plug to prevent spraying when the liquid content boils. The glass plates (P) minimize disturbance of the vapor level which reaches the h-h' point when the liquid boils.

Balance and Recording System:

The Dewar tube with its contents is

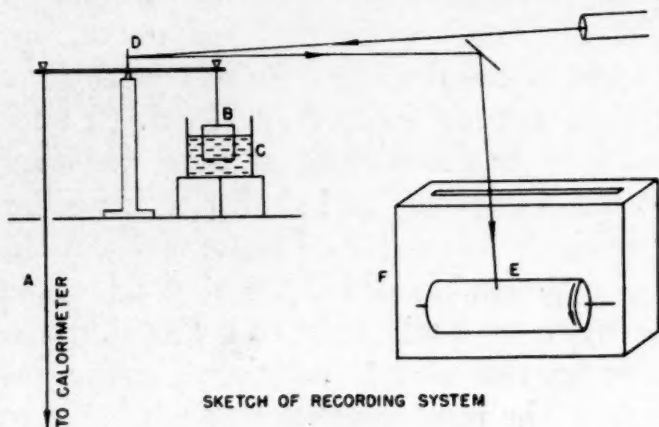


FIGURE 1

suspended in the calorimeter from a hook on the left arm of a balance situated on top of a case enclosing the calorimeter, as shown in Figure 2. On the right arm of the balance is suspended an aluminum cylinder (B) partially submerged in motor oil contained in a three-inch-diameter brass cup (C). This arrangement acts as a damper and sensitivity regulator, since cylinders of various diameters can be interchanged to give the desired sensitivity to the balance.

A small vertical mirror (D) is attached to the balance beam near the fulcrum to reflect a narrow beam of light, which is finally focused on photographic paper wrapped around a rotating drum (E). The drum has its axis parallel to the direction of motion of the light beam and is driven at constant speed by a synchronous motor. The recorder is properly shaded to permit operation without

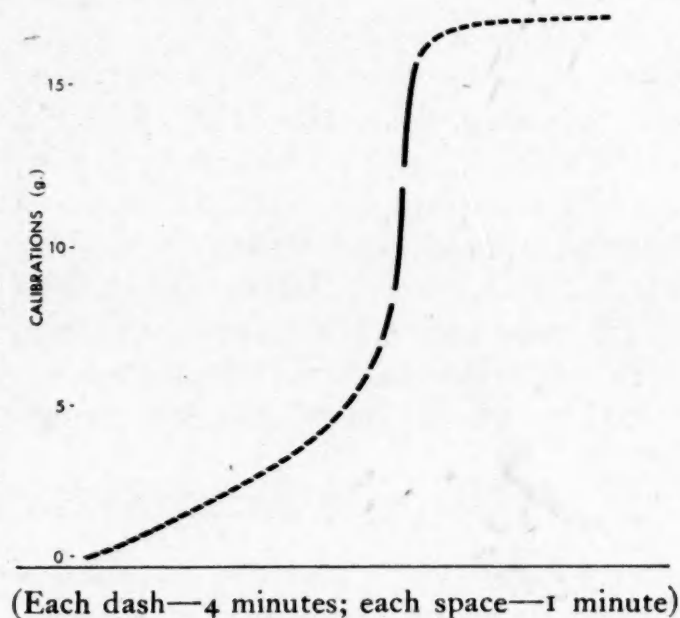


FIGURE 3

darkening the room. With a Wratten Filter No. 12 over the recorder slit, Kodak Linagraph 697 Paper was found suitable for our purpose.

Figure 3 is a sample of a recording obtained for a polymerization using methyl methacrylate with catalyst. The duration of this reaction was three and one-half hours.

SKETCH OF RECORDING SYSTEM

FIGURE 2